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GIANT-CELL GRANULOMA OF THE RESPIRATORY TRACT (WEGENER'S GRANULOMATOSIS)

BY

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This paper is based on a retrospective study of data from 10 patients who had in common an illness characterized by symptoms of progressive ulceration in the respiratory tract together with signs of widespread inflammatory disease. Histological examination of material from each case shows disseminated granulomata, most common in the respiratory tract and kidneys, and widespread vascular lesions similar to polyarteritis nodosa. The name Wegener's granulomatosis has been applied to this syndrome (Ringertz, 1947; Johnsson, 1948; Fahey *et al.*, 1954). The purpose of this paper is to describe in brief the clinical and pathological features, to give a concept of the pathogenesis, and to suggest a method of treatment. The cases, which were selected according to the pathological criteria of Godman and Churg (1954), have been described in detail elsewhere (Leggat and Walton, 1956; Walton, 1957).

Clinical Features

The main data from each case, and from 46 others selected from the literature, are summarized in Table I. An analysis of symptoms and signs is given in Table II. Typically, the disease occurs in previously healthy young or middle-aged adults of either sex. The onset is insidious, with non-specific symptoms of infection in some part of the respiratory tract. Two patterns can be distinguished. In about two-thirds of the cases persistent purulent rhinorrhoea is accompanied by nasal obstruction and crusting, antral pain, and epistaxis. Otorrhoea, deafness, or ulceration of the gums was the initial symptom in a few of these: each later developed rhinorrhoea. In the second, smaller group, attention is drawn to the lungs because of chronic cough, haemoptysis, or pleurisy. Often the constitutional upset is out of proportion to the apparent intensity of the local lesion, and the patient seeks advice because of persisting malaise, fever, or weakness.

The course is usually rapid and full of incident, progressing to death in, on average, five months, occasionally in as little as four weeks. A few patients (Cases 9, 19, 43, 45, and 47, Table I) have had a more chronic illness with periods of remission, and survival for up to four years. Though temporary improvement sometimes follows antibiotic treatment, the local lesion always persists. Spread of the inflammatory process leads to extensive mucosal ulceration and cartilaginous or osseous destruction in the nose and palate on the one hand, and to widespread pulmonary consolidation on the other. Spread through the upper air passages is often followed by conjunctivitis, dimness of vision, increased lacrimation, and exophthalmos, deafness, earache, and otorrhoea. The development of a sore mouth, hoarseness, or dysphagia has resulted in the discovery of ulceration in the fauces, pharynx, or larynx. Only twice (Cases 1 and 53) has the mucosal ulceration spread to involve the skin of the face.

Sooner or later signs of widespread inflammatory disease appear in every case: fleeting arthralgia, numbness and tingling in the limbs, sensory loss, muscle weakness or paralysis, and a haemorrhagic vesicular rash most frequent on the skin of the face, wrists, and elbows and the oral mucosa are all common. A pericardial friction rub or electrocardiographic changes occasionally indicate involvement of the heart; parotitis, orchitis, and prostatitis also occur. In the late stages fever, usually of septic type, is almost constant, and albuminuria, haematuria, cylinduria, and/or pyuria have indicated renal involvement in nearly every case.

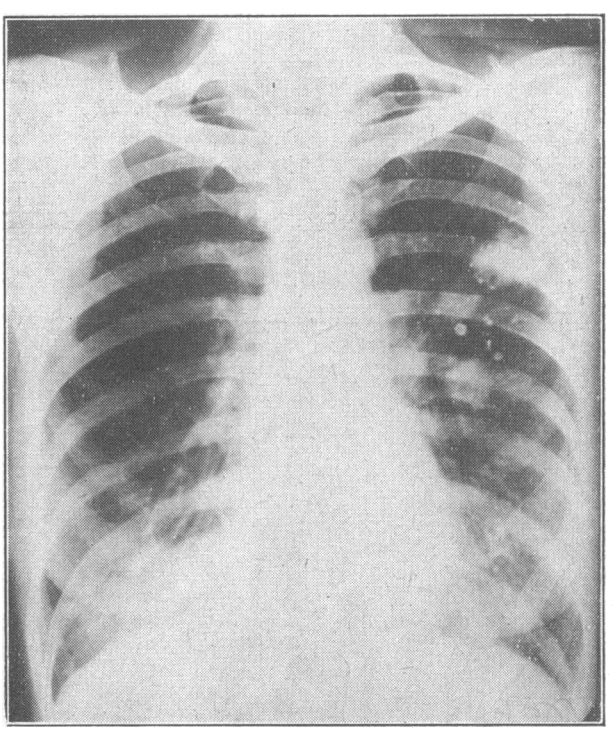

FIG. 1.—Case 10. Multiple rounded opacities are present in the left upper zone and both lower zones. Spicules of calcification are seen in the left upper zone.

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TABLE I.—*Clinical Features of 56 Cases of Wegener's Granulomatosis*

Case No.	Author	Description	Age and Sex	Onset	Duration Months	Initial Symptoms	Respiratory Tract Symptoms		Eye Changes	Ear Changes	Skin Rash	Joint Changes	Neuropathy	Other Organs	Urinary Changes	Cause of Death
							Upper	Lower								
1	Walton	Wegener's granulomatosis	39 M	1943	1½	Sore gums, limb pains	Epistaxis, rhinorrhoea	Cough	+	−	+	−	+	−	+	Respiratory failure
2	,,	,, ,,	33 M	1948	2½	Otorrhoea, nasal obstruction	Nasal block, epistaxis	Nil	−	+	+	−	−	−	−	? Uraemia
3	,,	,, ,,	34 F	1948	3½	Nasal block, joint pains	Purulent rhinitis	Stridor, dyspnoea	+	+	+	+	−	−	+	Respiratory failure
4	,,	,, ,,	42 F	1954	10	Pleurisy	Anosmia, oral ulceration	Productive cough	+	+	+	+	+	−	+	Circulatory failure
5	,,	,, ,,	62 M	1955	3	Dyspnoea	Nasal block, rhinitis	Dyspnoea	−	−	+	−	−	−	+	Uraemia
6	,,	,, ,,	52 M	1954	3	Deafness, sinusitis	Sore mouth	Cough, haemoptysis	−	+	−	+	−	−	+	Respiratory failure
7	,,	,, ,,	75 M	1955	1½	Cough, dyspnoea	Nil	Pain in chest	−	−	−	−	−	−	+	,, ,,
8	,,	,, ,,	56 M	1947	1	Malaise	,,	Nil	−	−	+	−	−	−	+	Uraemia
9	,,	,, ,,	73 M	1954	21+	Cough, joint pains	Hoarseness, sore throat	Haemoptysis	+	−	+	+	−	+	+	(Alive)
10	,,	,, ,,	42 F	1955	12+	Rhinitis with obstruction	Epistaxis	Productive cough	−	−	+	−	−	−	−	,,
11	Klinger (1931)	Periarteritis nodosa	70 M	1930	12	Sinusitis	Purulent rhinitis	Nil	+	−	−	+	−	−	+	? Uraemia
12	Rössle, 4 (1933)	Rheumatism	44 M	1931	9	Joint pains, septic illness	Rhinitis, dysphagia	,,	+	+	+	+	−	−	−	
13	Wegener (1936)	Rhinogenic granulomatosis	38 M	1934	5	Jaw pain, rhinorrhoea	Saddle nose, hoarseness	,,	−	+	+	+	−	−	+	Uraemia
14	,,	,, ,,	36 F	1935	6	Rhinorrhoea	Foul rhinorrhoea	Productive cough	−	−	+	−	−	−	+	Respiratory failure
15	,,	,, ,,	33 F	1933	3	Sanious rhinitis, headache	Fetor, gum bleeding	Nil	−	−	−	−	−	−	+	Uraemia
16	Postel and Laas (1941)	Periarteritis nodosa with lung changes	44 M	1939	4	Rhinorrhoea, epistaxis	Headache	Chest pain	−	−	−	−	−	−	+	,,
17	,, ,,	,, ,,	42 F	1940	1	Otorrhoea	Earache	Nil	−	+	−	−	+	−	+	,,
18	Banowitch *et al.*, 5 (1942)	Periarteritis nodosa	35 F	1936	8	Cough	Epistaxis	Productive cough	+	−	−	−	+	−	+	Cardiac failure
19	Staehelin (1942)	Sarcoidosis	20 F	1938	30	Dyspnoea, dysphagia	Sanious rhinitis, stridor	Purulent sputum	+	−	−	+	+	−	+	
20	Lindsay *et al.* (1944)	Chronic granuloma	67 F	1939	13	Saddle nose, epistaxis	Sanious rhinitis	Productive cough	−	−	−	−	−	+	+	Uraemia
21	Weinberg (1946)	Unknown granuloma and periarteritis nodosa	38 M	—	2	Sinusitis	Epistaxis, nasal block	Nil	−	−	+	−	−	−	−	Cardiac failure
22	,, ,,	,, ,,	50 F	—	—	Leg pains, sore throat	Nil	Cough, haemoptysis	−	−	+	−	+	−	+	Respiratory failure
23	Ringertz (1947)	Periarteritis nodosa; an unusual type	34 F	1945	8	Gum ulcer, cough	Nasal obstruction	Nil	−	−	−	−	−	−	+	Sepsis, cachexia
24	,, ,,	,, ,,	62 F	1947	3	Cough, fever	Nil	Productive cough	−	−	−	−	−	−	+	Uraemia
25	Johnsson (1948)	Wegener's granulomatosis	59 F	—	3	Deafness, earache	Otorrhoea	Nil	−	−	−	−	−	−	+	
26	Williams, 3 (1949)	Lethal midline granuloma	21 M	—	8	Sinusitis, fever	Epistaxis, otorrhoea	Chest pain, cough	−	+	+	−	−	−	+	Respiratory failure
27	McCart (1950)	Malignant granuloma	52 F	1948	4	Sinusitis	Sanious rhinitis	Nil	+	−	−	−	−	−	+	
28	,, ,,	,, ,,	52 M	1947	9	Rhinorrhoea, headache	Earache	,,	−	+	+	−	−	−	+	
29	Howells and Friedmann (1950)	Giant-cell granuloma	23 M	1949	5½	Rhinitis with obstruction	Gingivitis	,,	+	−	−	−	−	−	+	Uraemia
30	Mallory (1950)	,, ,,	69 F	1950	5	Cough with sputum	Nil	Productive cough	−	−	−	−	+	−	+	,,
31	Pugh (1950)	Complications of sinusitis	— M	1950	4	Deafness and headache	Nasal obstruction	,, ,,	+	+	−	+	−	−	+	Respiratory failure
32	Woodburn and Harris, 1 (1951)	Idiopathic nasal granuloma	31 M	1942	21	Nasal obstruction	Epistaxis, aphonia, fetor	Nil	−	+	+	−	−	−	+	
33	Ahlström *et al.* (1953)	Respirato-renal type of periarteritis nodosa	70 M	1948	2	Chest pain, dyspnoea	Nil	Pain, dyspnoea	−	−	−	−	−	−	+	Uraemia
34	,, ,,	,, ,,	41 F	1948	14	Sinusitis	Crusting and hoarseness	Pneumonia	+	−	+	+	−	+	+	,,
35	Straiton *et al.* (1953)	Nasal granuloma and periarteritis nodosa	49 M	1951	3	Rhinitis with obstruction	Epistaxis	Nil	+	−	−	−	+	−	+	Cardiac failure
36	,, ,,	,, ,,	51 M	1951	6	,, ,, ,,	Epistaxis, hoarseness	Cough	−	+	−	−	+	−	−	Uraemia
37	Fienberg (1953a)	Necrotizing granulomatosis of lungs	27 M	1950	7	Haemoptysis, chest pain	Epistaxis, stomatitis	Pain, haemoptysis	+	−	−	+	−	−	+	,,
38	,, ,,	,, ,,	54 M	1950	1½	Dyspnoea, cough	Nil	Cough, haemoptysis	−	−	−	+	−	−	+	Respiratory failure
39	Fahey *et al.* (1954)	Wegener's granulomatosis	40 F	1951	2	Sinusitis, atelectasis	Crusting	Nil	−	−	−	−	−	−	+	Uraemia
40	,,	,, ,,	34 M	1951	14	,, arthritis	Epistaxis	Nil	+	−	+	+	−	−	+	,,
41	,,	,, ,,	50 M	1950	3	Orchitis, weakness	Oral ulceration	Cough, chest pain	−	−	+	+	+	+	+	,,
42	,,	,, ,,	39 M	1949	5	Sinusitis	Rhinorrhoea	Nil	+	−	+	−	+	+	+	,,
43	,,	,, ,,	43 M	1933	48	Sinusitis, otitis	Hoarseness, saddle nose	,,	−	+	−	+	−	−	+	Septicaemia
44	,,	,, ,,	12 F	1953	1	Rhinorrhoea, sinusitis	Purulent rhinitis	Dyspnoea	+	+	+	−	−	−	+	Respiratory failure
45	,,	,, ,,	38 M	1951	39	Sinusitis, cough, pleurisy	Saddle nose	Nil	+	−	−	−	−	−	+	
46	McCallum (1954)	Nasal granuloma, periarteritis	31 M	1952	2	Sinusitis, fever	Purulent rhinitis	Chest pain	−	−	−	+	−	−	+	Uraemia
47	Seidelin and Willcox (1954)	Giant-cell granuloma and periarteritis nodosa	55 F	1944	40	Sanious rhinorrhoea	Oral ulceration	Nil	+	−	+	+	−	−	+	,,
48	,, ,,	,, ,,	54 M	1949	17	,, ,,	Nasal deformity	,,	−	−	−	−	+	−	+	Cardiac failure
49	,, ,,	,, ,,	59 F	1947	9	Bleeding from ear	Sinusitis	,,	+	+	+	+	−	−	+	Uraemia
50	Milner (1955)	Giant-cell granuloma	41 F	1954	2	Swollen gum, rhinitis	Dysphagia	,,	+	−	+	−	+	−	+	,,
51	Cogan, 2 (1955)	Wegener's granulomatosis	45 F	—	4	Coryza, hoarseness	Saddle nose	,,	+	−	+	−	+	−	−	Myocardial infarction
52	Bignami and Ficari (1956)	,, ,,	24 F	?1955	5	Earache	Purulent rhinitis	,,	+	+	+	+	−	−	+	
53	Morgan and O'Neil (1956)	,, ,,	26 M	1953	11	Gingivitis, neck ulcer	Loosening of teeth	,,	−	−	+	+	−	−	−	Myocardial infarction
54	Chatillon *et al.*, 3 (1956)	Wegener's angiitis	42 M	1955	6	Epistaxis, weight loss	Sinusitis	,,	+	−	+	+	−	−	+	Cardiac failure
55	Short, I (1957)	Stevens-Johnson syndrome	25 M	1949	1	Chest pain, cough	Nasal block, hoarseness	Cough, pain	+	−	+	−	−	−	+	
56	Rose and Spencer, 87 (1957)	Polyarteritis nodosa	49 M	1950	3	Fever, earache	Otorrhoea	Cough	−	+	−	−	+	−	+	Cardiac failure

Once signs of dissemination have occurred the general condition has always deteriorated and death has ensued from uraemia or secondary bronchopneumonia (Table I).

Clinical investigations of note are summarized in Table III. The radiological changes in the lungs are of particular interest. In just over half of the cases dense circular or oval opacities are present in one or more lobes (Fig. 1), often showing central cavitation, and varying in size up to that of a hen's egg. Less often bronchopneumonic infiltration is the only change of note.

TABLE II.—*Symptoms and Signs in 56 Cases of Wegener's Granulomatosis*

	No.	Per Cent.
Upper air passages	50	89·3
Rhinorrhoea and/or sinusitis	34	60·7
Nasal obstruction without rhinorrhoea	4	7·1
Epistaxis	18	32·1
Saddle nose	5	8·9
Gum pain or ulcer	7	12·5
Hoarseness	8	15·3
Dysphagia	3	5·4
Otorrhoea and/or deafness	18	32·1
Eyes	23	41·1
Conjunctivitis	17	30·4
Proptosis	5	8·9
Dimness of vision	3	5·4
Scleritis	6	10·7
Lungs	27	48·2
Cough	22	39·3
Haemoptysis	6	10·7
Pleural pain	11	19·6
Urinary tract	14	25·0
Oliguria	10	17·9
Haematuria	4	7·1
Skin rash	26	46·4
Polyarthritis	19	33·9
Peripheral neuritis	16	28·6

TABLE III.—*Clinical Investigations in 56 Cases of Wegener's Granulomatosis*

	No. of Cases Examined	Abnormal	
		No.	Percentage
Radiography:			
Skull: sinus opacities	21	18	85·7
Lung shadows	40	38	95·0
Round and discrete		23	57·5
Bronchopneumonic infiltration		10	25·0
Haematology:			
Microcytic anaemia	33	32	97·0
Leucocytosis	56	38	67·9
Eosinophil leucocytosis	37	17	45·9
Urine:			
Albumin	42	37	88·0
Erythrocytes	42	34	81·0
Leucocytes	42	21	50·0
Casts	42	28	66·7
Biochemistry:			
Uraemia	27	23	83·2
Hyperglobulinaemia	10	8	80·0
High blood pressure	33	8	24·2

No specific aetiological agent has been isolated in any case. From examination of sputum and nasal swabs in 24 cases, the only pathogens isolated were *Staphylococcus aureus* from 14, a haemolytic streptococcus from 7, *Streptococcus viridans* from 4, and pneumococci from 3. Culture for fungi was negative in five out of eight cases; in the others *Actinomyces bovis* (twice), *Candida albicans*, and a "leptothrix" were isolated. A positive blood culture, a positive blood Wassermann reaction, and isolation of tubercle bacilli have each been reported once, but otherwise these investigations have always been negative. Similarly, all agglutination tests have been negative.

Pathology

The most striking changes occur in the respiratory tract. Extensive ulceration, often widespread, with necrosis of underlying cartilage and bone, is present in the nose, paranasal sinuses, palate, pharynx, and/or glottis in about three-quarters of the cases (Table IV). Most also show multiple shallow ulcers in the trachea and bronchi. The lungs were abnormal in all but two cases (Nos. 20 and 50). Rounded nodular areas of consolidation, greyish white in colour, measuring up to 4 cm. in diameter, and sometimes showing central cavitation, are usually present in one or both organs. Less frequently pale miliary nodules scattered diffusely through all zones, or varying degrees of consolidation, are noted. Infarcts were described in Case 36 only.

TABLE IV.—*Sites of Respiratory Tract Ulceration in 56 Cases of Wegener's Granulomatosis*

	No.	Per Cent.
Nose and nasal sinuses	34	60·7
Mouth and pharynx	21	37·5
Tongue	7	12·5
Larynx	14	25·0
Trachea	17	31·5*
Bronchi	23	42·6*

* Per cent. of 54 cases.

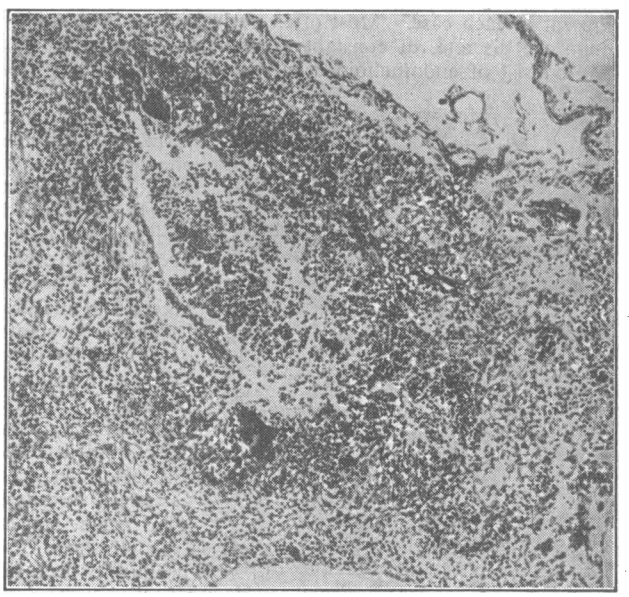

FIG. 2.—Case 3. Lung. (Haematoxylin and eosin. ×65.) A bronchiole showing intense granulomatous inflammation with early necrosis. Two giant cells of foreign-body type are present.

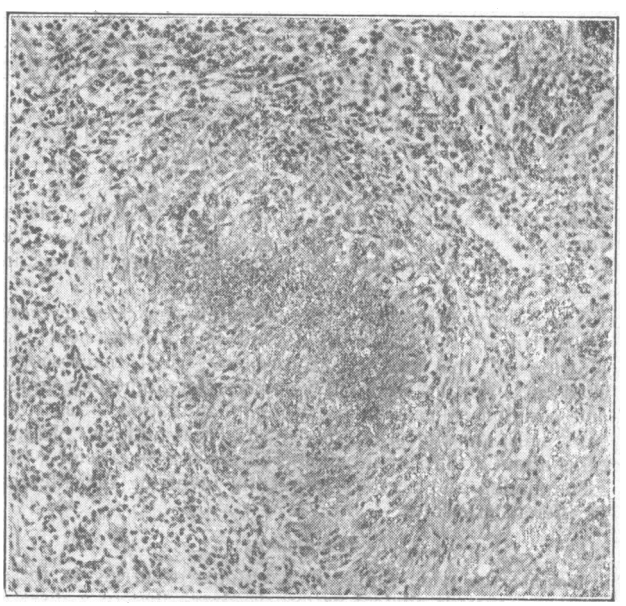

FIG. 3.—Case 7. Lung. (Haematoxylin and eosin. ×230.) Granuloma with numerous giant cells and extensive central necrosis.

Irrespective of their site, the lesions of the respiratory tract in my cases have a constant histological pattern (Fig. 2), that of granulomatous inflammation spreading deeply from the mucosa of the respiratory passages into the surrounding tissue. Intrapulmonary bronchial ulceration is especially common. Giant cells, of both Langhans and foreign-body type, are very numerous in the granulation tissue, and widespread necrosis often affects both cartilage and bone. Many of the pulmonary lesions are clearly peribronchiolar or prove so to be in serial section studies, and the rounded areas of consolidation visible macroscopically are seen to be conglomerate areas of peribronchial and peribronchiolar necrosis. Vessels near the lesions are implicated in the inflammation but show no features to suggest a specific vascular disease: thus the changes in these vessels are often confined to the segment next to the granulomatous focus. No micro-organisms can be demonstrated in appropriately stained sections of lesions in any of my cases.

In addition to the ulceration of the respiratory tract, widespread granulomata and foci of vascular necrosis are present in each case. Most often perivascular, the granulomata are discrete, of constant tuberculoid pattern (Fig. 3), and consist of endothelioid cells in radial arrangement and Langhans type giant cells with a sprinkling of lymphocytes, plasma cells, and both neutrophil and eosinophil polymorphonuclear leucocytes. Central necrosis of mature lesions is constant. The vascular lesions are focal, independent of the granulomata, and affect small arteries and arterioles, occasionally venules. The acute stages (Fig. 4) show "fibrinoid" necrosis of all layers, destruction of the muscle and elastica, mural thrombosis, and neutrophil infiltration. Healing lesions, present in most cases, show organization and recanalization of both the necrotic vessel wall and the luminal thrombus.

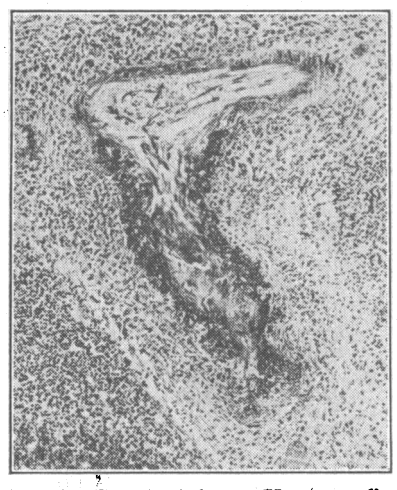

FIG. 4.—Case 4. Spleen. (Haematoxylin and eosin. ×90.) Pulp arteriole at a bifurcation. One limb shows acute "fibrinoid" necrosis and perivascular polymorph infiltration.

These widespread lesions, the incidence of which is given in Table V, are most frequent in lung, spleen, and kidney, though the number varies from case to case and organ to organ. Sometimes—for example, Cases 8 and 19—the granulomata are very numerous and visible as pale nodules about 0.1 cm. in diameter in many organs; in others the vascular lesions are very numerous, producing infarcts in kidney, spleen, heart, and testis.

The kidneys deserve special mention, having been severely affected in all but Cases 18, 30, and 45. Enlargement and blurring of the architecture are the usual macroscopic changes. Focal "fibrinoid" necrosis of glomerular loops and periglomerular granulomatous inflammation, often with giant cells, are almost constant histological findings. In my cases about a third of the glomeruli are usually affected, the inflammation and necrosis frequently involving the afferent or efferent arterioles.

Discussion

Despite the wide range of symptoms occurring in these cases, a constant clinical pattern is clear—that of a disease process beginning with symptoms and signs of an inflammatory lesion in the respiratory tract, continuing with evidence of widespread inflammation, and terminating in renal or respiratory failure. In most, especially Cases 4, 9, 10, 47, 48, and 49, the priority of the lesions of the respiratory tract is quite clear, and a definite time interval, of up to three years (Case 47), has often elapsed before the onset of widespread disease. In the early reports (Klinger, 1931; Rössle, 1933; Wegener, 1936, 1939) nasal lesions were prominent. Later authors (Postel and Laas, 1941; Weinberg, 1946; Ringertz, 1947; Johnsson, 1948; Godman and Churg, 1954), in describing cases in which tracheo-bronchial and pulmonary changes were more striking, noted their similarity to Wegener's cases. As each type shows similar local and widespread histological features, it is clear that they differ only in the level in the respiratory tract of the initial lesion. Furthermore, tracheo-bronchial or pulmonary lesions were present in all except Cases 20 and 50, and lesions in upper air passages may have been overlooked in some or all of the 12 cases in which such were not recorded.

TABLE V.—*Incidence of Disseminated Lesions in 54 Cases of Wegener's Granulomatosis*

	No.	Per Cent.
Discrete granulomata	54	100
Upper air passages	28	51·9
Trachea	10	18·5
Lungs	44	81·5
Spleen	30	55·6
Kidney	36	66·7
Liver	9	16·7
Lymph nodes	11	20·4
Heart	6	11·1
Prostate	4	7·4
Brain and meninges	4	7·4
Other organs	4	7·4
Focal necrotizing arteriolitis	54	100
Upper air passages	14	25·9
Lungs	47	87·0
Spleen	42	77·8
Kidney	42	77·8
Liver	10	18·5
Heart	15	27·8
Intestine	13	24·1
Skin	9	16·7
Adipose tissue	8	14·8
Voluntary muscle	8	14·8
Pancreas	5	9·3
Adrenal	6	11·1
Testis	5	9·3
Gall-bladder	4	7·4
Peripheral nerve	4	7·4

To date, including those of the present series, at least 56 cases which satisfy the diagnostic criteria of Godman and Churg (1954) have been reported, often as polyarteritis nodosa, malignant granuloma, or lethal midline granuloma. There can be little doubt, though, that the condition is more common than at first appears, as many cases have been excluded from the series only because of the absence of full data—namely, those of Siegmund (1936), Schürmann (1936), Moore *et al.* (1951), Rojas (1952), Geist and Mullen (Case 1, 1953), Breckenridge *et al.* (Case 3, 1954), Alexander (Case 3, 1954), Cutler (Case 2, 1955), Friedmann (Cases 4, 5, and 7, 1955), Paterson (Cases 1, 2, and 6, 1956), Rogers and Roberto (Cases 1 and 2, 1956), French and Civin (1956), Kelly (1956), McKibben and Bayliss (1956), Chatillon *et al.* (Cases 1 and 2, 1956), and Singh *et al.* (Cases 1 and 4, 1958), and others mentioned by Godman and Churg (1954). A further estimate of the frequency of the condition can be gained from the analysis of 104 cases of polyarteritis nodosa by Rose and Spencer (1957). Of these, one, Case 87, is a typical example of Wegener's granulomatosis, while four others, Cases 81, 82, 84, and 89, had granulomata of the upper respiratory tract and are almost certainly further examples.

Of the 56 cases, 33 have been male and 23 female. All age groups save the very young have been affected, the youngest patient being aged 12 years, the oldest 75, with the peak incidence in the fourth and fifth decades.

The pathological features of Wegener's granulomatosis were defined by Godman and Churg (1954). I believe, however, that the renal lesions are simply vascular and

granulomatous lesions as seen in other organs but modified by the local architecture. The basic pathological features of the syndrome are thus: first, giant-cell granulomatous ulceration at one or more levels in the respiratory tract; secondly, widespread giant-cell granulomata, discrete and frequent in lung, kidney, and spleen; thirdly, generalized necrotizing lesions of small vessels, again most common in lung, kidney, and spleen. The initial lesion is that in the respiratory tract, a granulomatous inflammation spreading from the mucosa, but there is little doubt that subsequent thrombosis of small vessels contributes to the development of the large necrotic areas in nares, glottis, and lung. The widespread granulomata resemble those found in experimental serum sickness (Rich, 1942), "allergic granulomatosis" (Churg and Strauss, 1951), and many cases of fatal drug sensitivity (Waugh, 1952; O'Brien and Storey, 1954; Rasmussen, 1955; and others). The necrotizing vascular lesions are morphologically similar to those in polyarteritis nodosa of the "microscopic" variety (Davson *et al.*, 1948), "hypersensitivity angiitis" (Zeek, 1952, 1953), and experimental hypersensitivity (Rich and Gregory, 1943; McKeown, 1947; Crawford and Nassim, 1951; Germuth *et al.*, 1955; and others).

As Fahey *et al.* (1954) have remarked, Wegener's granulomatosis closely resembles, both clinically and pathologically, several other uncommon diseases "which run in a spectrum from pure necrotizing and granulomatous processes without vasculitis through mixed forms to pure arteritis without granulomas." This close resemblance has led to many cases being described under a wide range of titles (Table I). Klinger (1931), Ringertz (1947), Ahlström *et al.* (1953), Rose and Spencer (1957), and others regarded their cases as variants of polyarteritis nodosa, whilst many authors have been impressed by the similarity of the local lesion in Wegener's granulomatosis with that in malignant granuloma of the nose (Woodburn and Harris, 1951; Geist and Mullen, 1953; Alexander, 1954; Friedmann, 1955; Paterson, 1956; Singh *et al.*, 1958). Furthermore, Fienberg (1955) was impressed by the similarity of his cases with Loeffler's syndrome and "allergic granulomatosis," and suggested that all three conditions be grouped as "pathergic granulomatosis." Yet neither in polyarteritis nodosa, malignant granuloma, Loeffler's syndrome, nor "allergic granulomatosis" is ulceration of the respiratory tract associated with widespread granulomata and vascular necrosis, and I agree with Godman and Churg (1954) in their comment, "The remarkable similarity of the pathological changes in all the cases . . . makes it probable that we are dealing with a peculiar and separate syndrome."

Early Course and Development

The early course in Wegener's granulomatosis is one shared by many diseases, ranging from tuberculosis to neoplasm. The diagnosis should be suspected whenever these can be excluded and destructive lesions in the respiratory tract persist despite antibiotic treatment. When evidence of widespread disease, such as haematuria, uraemia, polyarthritis, and peripheral neuritis, supervenes, the diagnosis is clear. Eosinophilia, conjunctivitis, the characteristic round shadows in chest radiographs, and a haemorrhagic skin rash are confirmatory features. The clinical diagnosis can be supported by biopsies from the ulcerative lesions, which are accessible in the upper air passages in three-quarters of the cases, and here eosinophilia, giant cells, and focal granulomata help in the differentiation from malignant granuloma. Biopsy of the skin lesions, which are micro-infarcts due to arteriolar thrombosis, is useful to demonstrate vascular necrosis. In patients in whom the initial or major lesion is in the lung, the obtaining of biopsy material by thoracotomy or bronchoscopy is justifiable in the early stages.

It is clear that two phases, sometimes merging but more often distinct, are involved in the development of Wegener's granulomatosis. The ulceration of the respiratory tract is primary, and the widespread lesions occur later in the natural history of the disease. As polyarteritis nodosa thus cannot be the primary disease, and as no specific micro-organism has yet been demonstrated, the aetiology is unknown. Most authors infer that an immunological reaction is involved. Fienberg (1953b) has suggested that the primary lesion is an Arthus phenomenon localized to the bronchial tree, and Kahn (1954, 1955) that the local ulceration is a reaction to an antigen circulating in the blood stream. Yet the evidence is incomplete and the aetiology of the primary lesion must still be regarded as uncertain.

In so far as the widespread, or secondary, lesions are concerned, there is considerable evidence that a hypersensitivity mechanism is involved. First, such a reaction is clearly the causal agent of similar or identical vascular and granulomatous lesions found in diseases such as scarlet fever (Hoyne and Steiner, 1940; Peale *et al.*, 1946) and other infections (Helpern and Trubek, 1933; Contratto, 1947; Bohrod, 1948), asthma (Wilson and Alexander, 1945; Teilum, 1946; Churg and Strauss, 1951), allergic dermatitis (Miale *et al.*, 1947; Rytand *et al.*, 1948), and serum sickness (Clark and Kaplan, 1937; Rich, 1942), in drug reactions (see above), or produced experimentally by measures designed to induce hypersensitivity in animals (see above). Secondly, many of the features of the terminal illness, such as the purpuric skin rash and stomatitis, migratory arthritis, eosinophilia, and transient pareses, are well known to occur in hypersensitivity states (Rich, 1946–7). Thirdly, the raised serum globulin level suggests an antibody response. Finally, impressive evidence came from Case 4, in which symptoms and signs of widespread disease appeared only during and after hypersensitivity reactions to streptomycin (Leggat and Walton, 1956). Widespread lesions morphologically similar to those in the other cases were found at necropsy, but were absent from a lung biopsy made before streptomycin therapy had begun. It is therefore probable that the secondary lesions in Wegener's granulomatosis are due to a hypersensitivity reaction, a drug (Cases 4, 5, 37, and 38) or tissue breakdown products being possible antigens.

Treatment

Many forms of empirical therapy have been unsuccessful. The temporary improvement that sometimes follows antibiotic treatment is probably due to control of secondary infection. Steroids occasionally produce remission (Case 45; Moore *et al.*, 1951; Cutler, 1955), but are more often ineffectual (Cases 39 and 52; Alexander, 1954; Bandler and Campbell, 1954; Paterson, 1956). I believe that the treatment of choice is radiotherapy to the local lesion, with control of secondary infection by suitable antibiotics, and that steroids should if possible be withheld until the local lesion has healed, owing to the danger of hindering the defence against infection of the open respiratory lesions.

Many cases of healing of malignant granuloma of the nose following *x* rays in low dosage have been reported, and it is logical to try this method on the very similar local lesion in Wegener's granulomatosis. The palatal and nasal lesions in my Cases 9 and 10 were thus healed, and Seidelin and Willcox (1954) and Singh *et al.* (1958) also report success with radiotherapy.

Steroids are the treatment of choice for the widespread lesions once the ulceration of the respiratory tract is healed. They reduce the antibody response (Bjørneboe *et al.*, 1951), inhibit the development of vascular lesions in sensitized animals (Rich *et al.*, 1950; Seifter *et al.*, 1950; Germuth and Ottinger, 1950; and others) and appear to induce healing of the vascular lesions in polyarteritis nodosa (Baggenstoss *et al.*, 1951; Symmers and Litchfield, 1952). The signs of widespread inflammation in Case 9 disappeared following cortisone therapy, the nasal and laryngeal lesions already having been healed by radiotherapy, and the patient has remained well for nearly two years. Cortisone also produced remission of symptoms in Case 10.

Conclusions

The constant clinical course and the presence in all cases of standard anatomical features suggest that the condition under discussion is a separate entity, even though it is closely linked, both morphologically and pathogenetically, with malignant granuloma, periarteritis nodosa, and other granulomatous and vascular diseases. Though the first cases recorded were those of Klinger (1931) and Rössle (1933), it was Wegener (1936, 1939) who first described the disease in detail, and it has come to be known as Wegener's granulomatosis. Including my 10 cases, at least 56 are on record, but many others, less well documented, are probable further examples of the disease.

The natural history clearly has two phases. Beginning with symptoms of chronic nasal or pulmonary infection, it continues with evidence of widespread inflammation. Though a few cases have lived for up to four years, in the majority death rapidly ensues from renal or respiratory failure, the average course being about five months. The clinical diagnosis, though difficult in the early stages, can be confidently made whenever to an ulcerative lesion in the respiratory tract is added evidence of widespread inflammatory disease. The radiological changes in the lungs are typical, and eosinophilia and biopsy of the local lesion or of skin are of confirmatory value.

The diagnostic pathological features are granulomatous ulceration at any level in the respiratory tract and widespread giant-cell granulomata and necrotizing lesions of small vessels. The characteristic round or oval consolidations in the lungs are not infarcts but conglomerate areas of peribronchial necrosis. The severe and constant changes in the renal corpuscles are focal, do not represent diffuse glomerulonephritis, but are simply granulomatous and vascular lesions modified by the local architecture.

The initial lesion in Wegener's granulomatosis is not polyarteritis nodosa, but the ulceration in the respiratory tract, the aetiology of which is uncertain. The widespread lesions occur later in the course of the disease and there is impressive evidence that they are the result of a hypersensitivity reaction. Treatment should be primarily directed towards healing of the initial lesion, and radiotherapy has proved successful in some cases. Administration of cortisone or other steroids is the treatment of choice once widespread lesions have occurred.

Summary

Wegener's granulomatosis is an uncommon syndrome in which giant-cell granulomata in the respiratory tract occur together with granulomatous and vascular lesions resembling those in polyarteritis nodosa. In this work, which is based on a study of 10 cases, and 46 others selected from the literature, the clinical and pathological features are described and tabulated.

The disease is clearly a separate entity, differing both clinically and in the character and distribution of the lesions from similar conditions, such as polyarteritis nodosa and malignant granuloma. It begins as a progressive ulceration of unknown aetiology in the respiratory tract. Sooner or later widespread lesions, the result of a hypersensitivity reaction, complete the disease picture. Treatment of the lesions of the respiratory tract by radiotherapy has been successful in a few cases.

ADDENDUM.—Since this paper was written, I have seen further reports of cases of Wegener's granulomatosis by Fanger and Hoffman (1957), Plummer *et al.* (1957), Levine and Madden (1957), Read and Treip (1957), Stoeckle *et al.* (1957), and Gordon *et al.* (1957).

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